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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/003,630	10/29/2001	Philip C. Wong	JHU1690-2	6218

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EXAMINER	
BERTOGLIO, VALARIE E	

ART UNIT	PAPER NUMBER
1632	

DATE MAILED: 10/03/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/003,630	WONG ET AL.	
	Examiner	Art Unit	
	Valarie Bertoglio	1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *08 August 2003* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-56* is/are pending in the application.

4a) Of the above claim(s) *1-33 and 41-56* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *34-40* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *29 October 2001* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☒ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

Election/Restrictions

Applicant's election of GroupXVIII, claims 34-40 in the election filed 08/08/2003 is acknowledged. Because applicant did not distinctly and specifically point out the supposed errors in the restriction requirement, the election has been treated as an election without traverse (MPEP § 818.03(a)). Claims 1-56 are pending. Claims 1-33 and 41-56 are withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected invention, there being no allowable generic or linking claim. Claims 34-40 are currently under consideration.

Claim Objections

Claim 34-40 are objected to as containing subjected matter that is drawn to a non-elected invention. The elected invention is drawn to a method of identifying an agent that modulates the expression or activity of BACE1 by comparing the phenotype of a transgenic Aβ1–42 organism contacted with the agent to that of a BACE-1 knockout organism.

Claim Rejections - 35 USC § 112-1st paragraph

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 34-40 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not

described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Vas-Cath Inc. v. Mahurkar, 19USPQ2d 1111, clearly states that "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession *of the invention.* The invention is, for purposes of the 'written description' inquiry, *whatever is now claimed.*" (See page 1117.) The specification does not "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed." (See *Vas-Cath* at page 1116).

The claimed invention as a whole is not adequately described if the claims require essential or critical elements that are not adequately described in the specification and that is not conventional in the art as of applicants effective filing date. Possession may be shown by actual reduction to practice, clear depiction of the invention in a detailed drawing, or by describing the invention with sufficient relevant identifying characteristics such that a person skilled in the art would recognize that the inventor had possession of the claimed invention. Pfaff v. Wells Electronics, Inc., 48 USPQ2d 1641,1646 (1998).

Claims are drawn to a method of identifying an agent that modulates BACE1 using both a BACE1 knockout organism (claim 34) and an organism (claims 34 and 37-40), particularly a transgenic organism (claims 35 and 36) wherein the transgenic organism is transgenic for overexpression of Aβ1-42 (claim 36). The claims encompass all species of organisms. However, the specification only describes a knockout mouse deficient for BACE-1. The specification does not describe any other species of BACE1 knockout organism or any organism encompassed by

claim 34 or any transgenic organism encompassed by claims 35 and 36. There is no description in the art about the phenotype of any non-mouse species of organism comprising a knockout of the BACE1 gene or of any species of transgenic organism that overexpresses of Aβ1-42.

In analyzing whether the written description requirement is met, it is first determined whether a representative number of species have been described by their complete structure. Since it is not realistic to expect that the "complete structure" of any transgenic organism, or even a cell, could be described, this requirement is interpreted to be whether phenotypic consequences of altering the genotype have been described. In the instant case, the claimed invention encompasses 1) organisms comprising a knockout of the BACE1 gene and 2) transgenic organisms overexpressing Aβ1-42. In the instant case, the claimed embodiments of organisms comprising a BACE1 knockout or an Aβ1-42 transgene encompassed within the genus lack a written description. The specification fails to describe the species that fall into this genus and it was unknown as of Applicant's effective filing date that the organisms embraced by the claims would have the desired properties. The skilled artisan cannot envision the detailed chemical structure of the encompassed organisms, and therefore conception is not achieved until reduction to practice has occurred, regardless of the complexity or simplicity of the method of isolation. Adequate written description requires more than a mere statement that it is part of the invention and reference to a potential method of creating it.

While the claimed invention encompasses transgenic organisms derived through targeted gene insertion as well as random transgene integration, the phenotype(s) of the claimed organisms cannot be predicted because the art of making knockout and transgenic organisms is highly unpredictable. Wood (2000, Comparative Medicine, Vol. 50, pages 12-15) noted:

"The phenotype of an animal is determined by a complex interaction of genetics and environment. It is the evaluation of the phenotype that allows us to determine the usefulness of a mutant strain as a model for biomedical research……A specific phenotype is usually expected from genetically altered mice whether they are transgenic over-expression models or gene knockout models where a particular gene function has been modified or ablated altogether. Thus for any given genetic alteration, we often try to predict what the phenotype will be. Many times we find the predicted phenotypes or more. It is, however, common to hear that surprisingly a given model has 'no phenotype'."

Therefore, the limited disclosure in the specification is not deemed sufficient to reasonably convey to one skilled in the art that Applicants were in possession of the genera recited in the claims at the time the application was filed. Thus it is concluded that the written description requirement is not satisfied for the claimed genera.

Applicant is reminded that *Vas-Cath* makes clear that the written description provision of 35 U.S.C. §112 is severable from its enablement provision (see page 1115).

Claims 34-40 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

Claims are drawn to a method for identifying an agent that modulates the expression or activity of BACE1 comprising administering an agent to a first test organism and comparing the phenotype of the first test organism to that of a BACE-1 knockout organism not contacted with the agent, whereby a phenotype substantially equal to the BACE-1 knockout organism is

indicative of an agent that modulates BACE-1 activity. Claims limit the first test organism to a transgenic organism (claim 35) comprising a transgene causing overexpression of Aβ1-42 (claim 36)

The specification describes generating a BACE1 knockout mouse generated by targeted gene insertion into the mouse BACE-1 gene. The specification teaches that the mouse lacks the APP cleavage products Aβ1-40/42 and Aβ11-40/42. The specification contemplates that the BACE-1 knockout mouse can be used as a control, or baseline, for comparison with mice expressing BACE-1 that have been treated with an agent that is a candidate for having BACE-1 modulatory activity (page 5, last paragraph). This assay is based on the premise that if the agent suppresses BACE-1 expression or activity in an organism that normally expresses BACE1, then that organism will phenotypically resemble the BACE-1 knockout organism.

1) The specification fails to enable making a BACE1 knockout organism for any species other than mouse. The breadth of the claims is such that any species of organism is encompassed. The claimed method compares the phenotype of an organism (claims 34 and 37-40), particularly a transgenic organism expressing Aβ1-42 (claims 35 and 36), that is treated with an agent to the phenotype of an untreated BACE1-knockout organism. The specification teaches targeting the BACE-1 gene in mouse ES cells and using the gene-targeted ES cells to generate chimeric mice comprising cells with a targeted disruption in the BACE-1 gene and mating the chimeras to generate germline transgenic BACE-1 knockout mice (paragraphs 0167-0168). The specification does not teach how to perform gene targeting to generate a knockout organism in any species other than mouse.

The art at the time of filing held that targeted gene insertion technology was not well-established for any species other than mouse. Since homologous recombination is required for gene targeting methods, cells in culture must be used to carry out the method. To generate a non-chimeric organism from the recombinant ES cells, the cells must be capable of contributing to the germ line. Mullins (1996, J. Clin. Invest., Vol. 98, pages S37-S40) teach that non-mouse ES cells capable of providing germline chimeras were not available (page S38, column 1, first paragraph). Campbell and Wilmut (1997, Theriogenology, vol. 47, pp, 63-72) acknowledge reports of ES-like cells in a number of species, but emphasize that as yet there are no reports of any cell lines that contribute to the germ line in any species other than mouse (page 65). Therefore, one of skill in the art would not know how to generate a knockout organism for any species other than mouse because totipotent ES cells that contribute to the germline of those species were not known.

2) The specification fails to teach how to make a BACE1 knockout organism that displays any phenotype as encompassed by claim 34 and further fails to recite a phenotype for the BACE-1 knockout organism that is to be used in assessing the effects of the test agent on an organism as set forth in claim 34. The specification teaches that the secretion of Aβ peptides (Aβ1-40/42 as well as Aβ11-40/42) from neurons is abolished in cultures of BACEl-deficient embryonic cortical neurons derived from BACE1- knockout mice (paragraph 0182) and that Aβ1-40 and Aβ1-42 were not detected in the cell culture from astrocytes isolated from BACE1-/- mice (paragraph 0190). The specification does not teach any other phenotype for the mice or indicate what phenotype(s) one of skill in the art would assay to determine if an agent is modulating BACE-1 in an organism by comparing the treated organism to an untreated BACE-1

knockout. Furthermore, the claims do not recite a phenotype for the BACE-1 knockout to be used as a means for comparison. As such, the claims may be interpreted to encompass BACE1 knockout organisms with any phenotype.

At the time of filing, the phenotype of transgenic knockout mice was unpredictable. Leonard (1995, Immunological Reviews, Vol. 148, pages 98-113) disclosed mice with a disruption in the g_c gene that was intended to be a model for X-linked severe combined immunodeficiency (XSCID), but display a variety of unexpected traits (abstract). These knockout mice were expected to have thymocytes with decreased proliferation in response to stimulation with antibodies, but the thymocytes proliferated normally (page 105, line 7). Griffiths (1998, Microscopy Research and Technique, Vol. 41, pages 344-358) taught that, despite a known role for the PLP gene based on spontaneous mutations in the gene, the knockout mouse failed to display any of the expected phenotypes (page 350, last paragraph). With respect to the instant invention, Luo (March 2001, Nature Neuroscience, Vol. 4, pages 231-232) taught that BACE1 deficient mice have a normal phenotype (paragraph bridging pages 231-232; Figure 1; and page 232 last 2 paragraphs). Luo et al. found the viability and normal phenotype of BACE1 knockout mice to very surprising, highlighting the phenotypic unpredictability set forth in the more general art. Thus, at the time of filing, the phenotype of a BACE-1 knockout organism, was unpredictable.

The specification fails to teach how one of skill in the art at the time of filing would generate a knockout organism, including a mouse, comprising a disruption in the BACE1 gene wherein the organism has any phenotype as encompassed by the claims. The specification fails to teach what phenotype of the knockout mouse should be used as a comparison for organisms

treated with an agent in the claimed methods. Because the phenotype of transgenic organisms is unpredictable, one of skill in the art would not know what phenotype to expect when making the claimed transgenic organism. It would require one of skill in the art at the time of filing, undue experimentation to determine how to make and use any species of organism comprising a genetic disruption of the BACE1 gene wherein the organism exhibits any phenotype as broadly claimed.

4) The specification fails to teach an Aβ1-42 transgenic organism of any species. As set forth above, the phenotype of a transgenic organism of any species, including mouse, is unpredictable. With respect to the instant invention, Staufenbiel (November 10-15, 2001, Society for Neuroscience Abstracts, Vol. 274, page 926) taught that secreted Aβ1-42 is hardly detectable in Aβ1-42 transgenic mice and that the mice do not develop amyloid plaques even beyond 24 months. Thus, mere expression of the Aβ1-42 transgene did not generate the desired effects. The purpose of using an Aβ1-42 transgenic organism in the claimed methods is to exacerbate the conditions associated with Alzheimer's disease (increased secretion of Aβ1-42 and increased formation of amyloid plaques) for the purpose of screening for agents that can ameliorate these effects of the transgene and phenocopy the BACE1 knockout which fails to produce said effects at all. The specification fails to provide any working examples teaching how one would make the Aβ1-42 transgenic organisms claimed. The specification fails to even provide general teaching of how one would make the Aβ1-42 transgenic organisms such that they would exhibit a phenotype useful in the claimed methods. Given the lack of guidance provided by the instant specification, it would require one of skill in the art undue experimentation to determine how to make and use the claimed invention.

5) The specification fails to teach phenotypes associated with Alzheimer's disease as broadly claimed (claim 40). The specification defines phenotypes associated with Alzheimer's disease to include "the appearance in an organism of a progressive formation of insoluble amyloid plaques and vascular deposits of the 4 kDa amyloid β-peptide. In addition, the phenotype can result in organisms displaying impaired performance on memory learning tests and abnormal neuropathology in a cortico-limbic region of the brain" (paragraph 0158). The specification does not teach other phenotypes associated with Alzheimer's disease. Furthermore, the specification does not teach that the organism of claim 34 has any of these above mentioned phenotypes as listed in the specification. The specification lacks the guidance necessary to obtain an organism with any of the phenotypes listed in the specification or all of the phenotypes encompassed by the claim. Therefore, one of skill in the art would not know how to obtain an organism exhibiting the broad genera of phenotypes encompassed by claim 40.

6) The specification fails to enable identifying an agent that "modulates" BACE-1 activity. The claims encompass agents that both increase and decrease BACE1 activity or expression. The claimed methods are directed to identifying an agent that produces a phenotype "substantially equal" to that of a BACE-1 knockout. Any agent identified through this means would be one that inhibits BACE-1 expression or activity, not increases its expression or activity. Therefore, claims should be limited to identifying an agent that inhibits BACE-1 expression or activity.

7) The specification fails to teach the method of claim 40 wherein the phenotype of the agent-treated organism of claim 34 is associated with Alzheimer's disease. Claim 34 requires that the treated organism have a phenotype substantially equal to that of the BACE1 knockout.

The specification teaches that the BACE1 knockout mouse fails to produce Aβ fragments, the presence of which is a phenotype normally associated with Alzheimer's disease. Thus, BACE1 knockout mice have a phenotype opposite that which is associated with Alzheimer's disease. Claim 40, however, adds the limitation that the organism that is administered the agent exhibits a phenotype associated with Alzheimer's disease. If the organism has a phenotype associated with Alzheimer's disease (claim 40), it cannot have a phenotype substantially equal to that of the BACE1 knockout as set forth by claim 34. The specification does not teach how to identify an agent that modulates BACE1 comprising administering the agent to an organism and comparing the phenotype of the organism with that of a BACE1 knockout whereby a phenotype substantially equal to that of the BACE1 knockout is indicative of an agent that modulates BACE1 wherein the organism exhibits a phenotype associated with Alzheimer's disease.

Therefore, in view of the quantity of experimentation necessary to determine the parameters listed above, the lack of direction and/or guidance provided by the specification, the undeveloped art with respect to totipotent ES cells from species other than mouse, the unpredictability of phenotype of transgenic organisms, and the breadth of the claims with respect to the phenotype of the organisms claimed, it would have required undue experimentation for one skilled in the art to make and use the claimed invention with a reasonable expectation of success.

Claim Rejections - 35 USC § 112-2nd paragraph

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 34-40 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

The term "substantially equal" in claim 34 is a relative term which renders the claim indefinite. The term " substantially equal " is not defined by the claim, the specification does not provide a standard for ascertaining the requisite degree, and one of ordinary skill in the art would not be reasonably apprised of the scope of the invention.

Conclusion

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Valarie Bertoglio whose telephone number is 703-305-5469. The examiner can normally be reached on Mon-Weds 6:00-2:30.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Deborah Reynolds can be reached on 703-305-4051. The fax phone number for the organization where this application or proceeding is assigned is (703) 872-9306.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703-308-1234.

PETER PARAS
PATENT EXAMINER

Valarie Bertoglio
Examiner
Art Unit 1632